

Rare Tumors at COG

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Retinoblastoma (RB)



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https://commons.wikimedia.org/wiki/File%3ARb_whiteeye.PNG

RB Background

- Less than 3% of US children under 15 diagnosed with cancer have RB
- In the first year of life it makes up 11%
- 2/3's of cases occur in those under 2
- 95% of cases occur in those under 5
- Incidence remains unchanged in the US over the 1975 to 1995 period
 - Balanced between whites and blacks
 - Balanced between males and females
 - 3.7 cases per million children
 - That means about 350 cases in the US per year (of 5-8k worldwide per year)

RB History

- Peru sculpture of about 2000 years ago may show RB
- Greek sculpture shows a lesion of the right eye (Meyer-Steineg collection from the Island of Kos)
- Western written: Peter Pauw's notes from 1597 about a 3yo boy with a large ocular tumor that was rapidly growing.
- First published bilateral case: Hayes in 1767.
- Around the same time James Wardrop championed enucleation (London).
- The first likely use of radiation was by Hilgartner in Austin, TX in 1903.



Photo: M. Isidro, M. Roque, T. Aaberg, B. Roque at <http://emedicine.medscape.com/article/1222849-treatment>

RB – Early RT Cases

- Hilgartner – 1903 – Bilateral. Treated with 84 fractions. LTFU.
- Schonberg – Three papers looking at a 2yof with bilateral disease
 - Advanced- enucleation
 - Less advanced eye- radiation
 - At 10 years – useful vision
 - At 15 years - useful vision
 - At 25 years, a secondary sarcoma that spread and killed her
- Verhoeff – bilateral treated in 1917
 - The child did well until 1977, a basal cell developed on the lid, later a squamous cell (that date is not a typo)

RB- Pathway

- Part of the classic “two hit hypothesis” (not covered here).
- Genetic pathway is relatively simple.

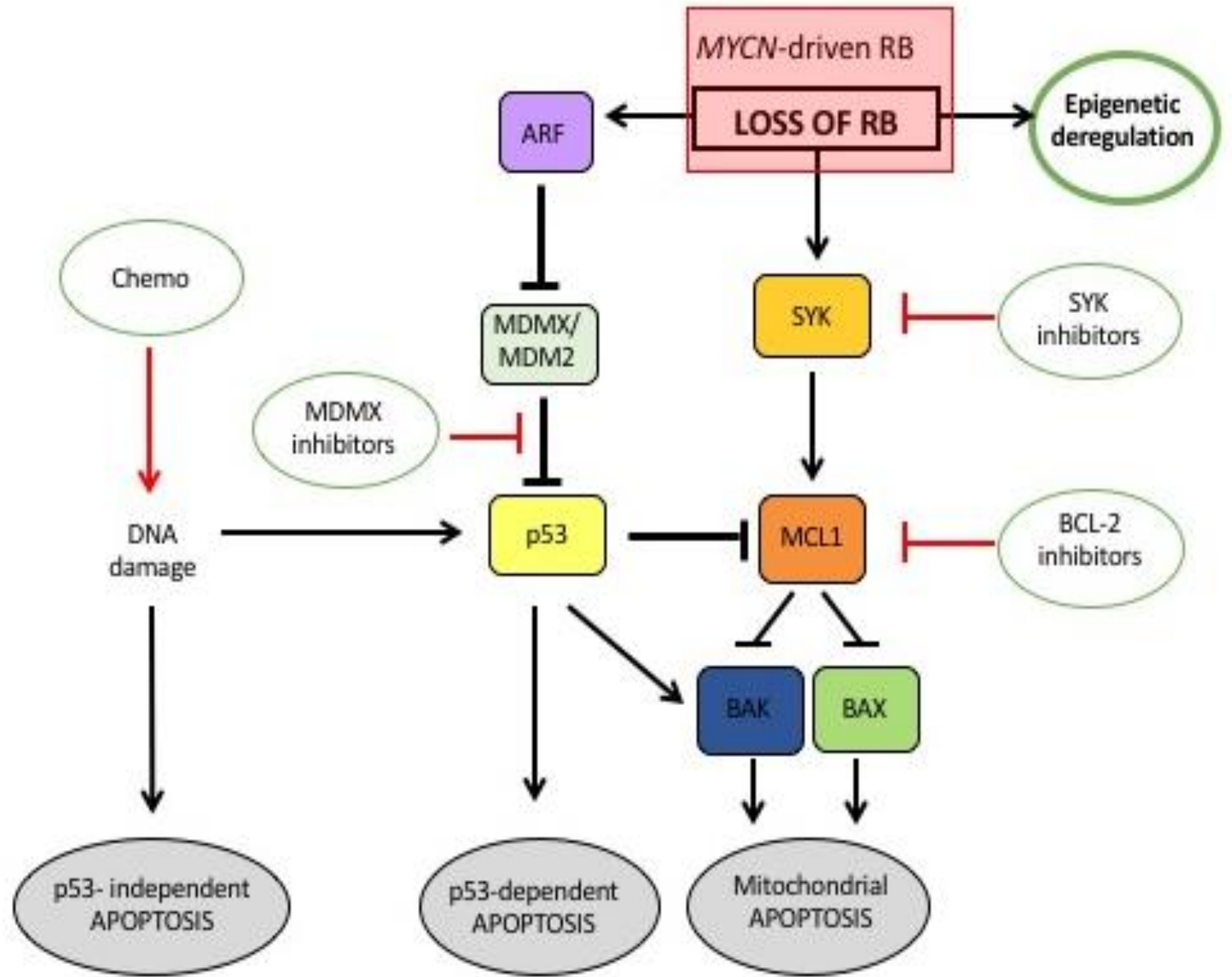
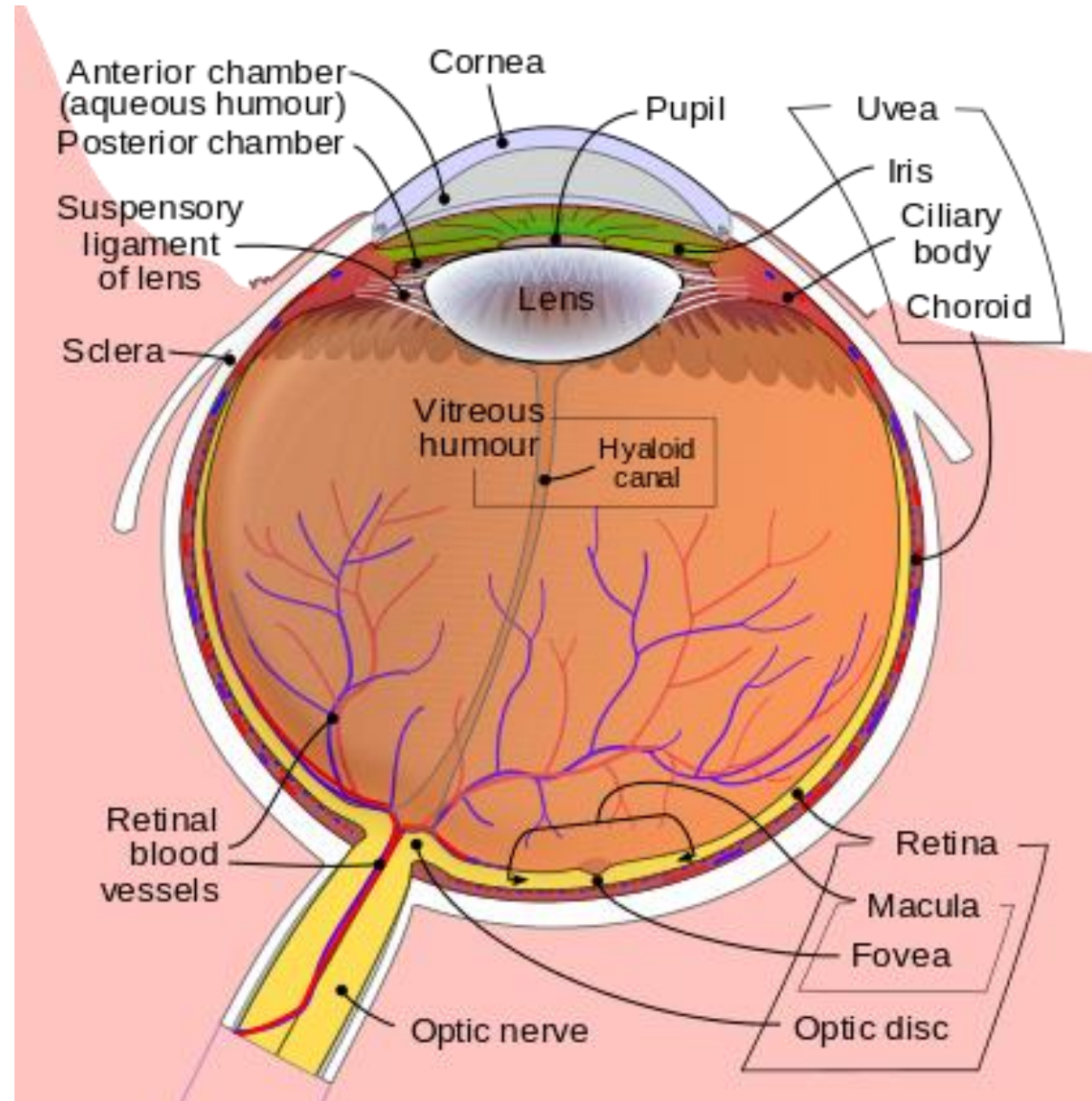


Figure kindly provided by Carlos Rodriguez-Gallindo

RB- Anatomy

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[https://commons.wikimedia.org/wiki/
/File%3ASchematic_diagram_of_the_
human_eye_en.svg](https://commons.wikimedia.org/wiki/File%3ASchematic_diagram_of_the_human_eye_en.svg)



RB – Reese-Ellsworth Staging System

Reese-Ellsworth Classification for Conservative Treatment of Retinoblastoma		
Group	Likelihood of Globe Salvage	Features
I	Very favorable	a) Solitary tumor, less than 4 disc diameters in size, at or behind the equator
		b) Multiple tumors, none more than 4 disc diameters in size, all at or behind the equator
II	Favorable	a) Solitary tumor, 4 to 10 disc diameters in size, at or behind the equator
		b) Multiple tumors, 4 to 10 disc diameters in size, at or behind the equator
III	Doubtful	a) Any lesion anterior to the equator
		b) Solitary lesion larger than 10 disc diameters behind the equator
IV	Unfavorable	a) Multiple tumors, some larger than 10 disc diameters in size
		b) Any lesion extending anterior to the ora serrata
V	Very unfavorable	a) Massive tumors involving over half of the retina
		b) Vitreous seeding

RB - International Classification System

Shields, C.L., et al., *The International Classification of Retinoblastoma predicts chemoreduction success*. Ophthalmology, 2006. **113**(12): p. 2276-80.

The International Classification (Staging) System for Retinoblastoma			
Group	Subgroup	Features	Details
A	A	Small Tumor	Small tumors ≤ 3 mm in basal diameter or thickness and without Group B features.
B	B	Larger Tumor	Tumors > 3 mm in basal diameter or thickness.
		Near Disc (Juxtapapillary)	Distance to disc ≤ 1.5 mm.
		Macular (near fovea)	Distance to fovea ≤ 3 mm.
		Subretinal Fluid	Clear subretinal fluid ≤ 3 mm to margin.
C		Focal Seeds	Tumor with:
	C1		Subretinal seeds ≤ 3 mm away.
	C2		Vitreous seeds ≤ 3 mm away.
	C3		Both C1 and C2.
D		Diffuse Seeds	Tumor with:
	D1		Subretinal seeds > 3 mm away.
	D2		Vitreous seeds > 3 mm away.
	D3		Both D1 and D2.
E	E	Extensive Disease	Occupying over 50% of the globe. Neovascular glaucoma. Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space. Invasion of postlaminar optic nerve, choroid (> 2 mm), sclera, or anterior chamber.

RB- International Staging System (with surgical data)

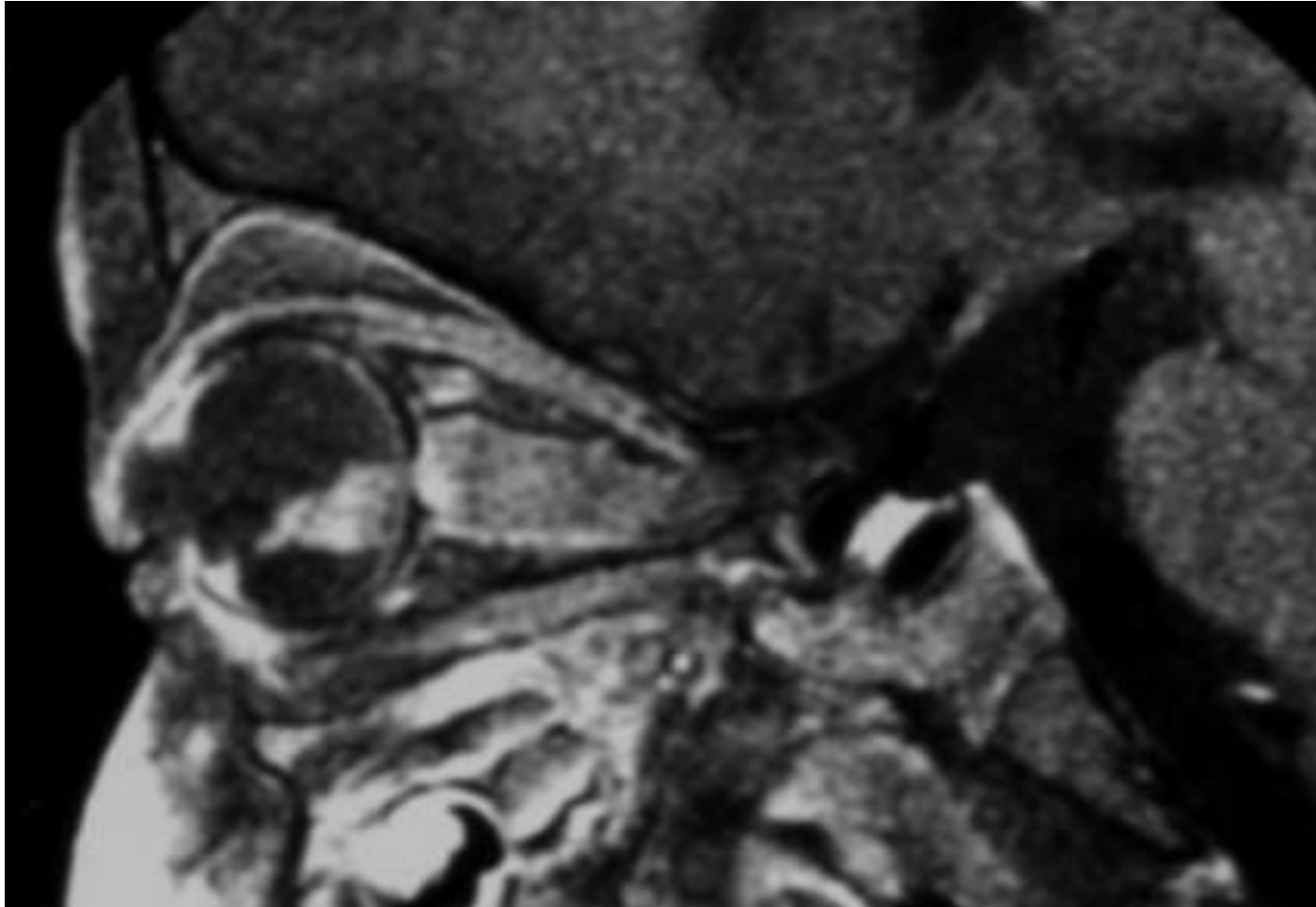
Chantada, G., et al., *A proposal for an international retinoblastoma staging system*. *Pediatr Blood Cancer*, 2006. **47**(6): p. 801-5.

International Classification of Retinoblastoma			
Stage	Likelihood of Globe Salvage	Features	
0	Treated Conservatively		
I	Eye enucleated, completely resected histologically		
II	Eye enucleated, microscopic residual tumor		
III	Regional extension	a) Overt orbital disease b) Preauricular or cervical lymph node extension	
IV	Metastatic Disease	a) Hematogenous metastasis (without CNS involvement)	1. Single lesion
			2. Multiple lesions
		b) CNS extension (with or without any other site(s) of regional or metastatic disease)	1. Prechiasmatic lesion
			2. CNS mass
	3. Leptomeningeal and CSF disease		

RB – Treatment (super condensed)

- Surgery
- Non-radiation local therapies (cryo, laser, etc.)
- Chemotherapy
 - IV (see COG trials over the last two decades)
 - Intra-arterial (Japan, MSKCC, now COG)
- RT (historic dose has been 45 Gy at 1.8 Gy/fx)
 - EBRT
 - Photon
 - Particles
 - Plaques (brachytherapy)
 - Nuances: Stage II-IV, see ARET0321. Even CSI is used in some cases (trilateral...)

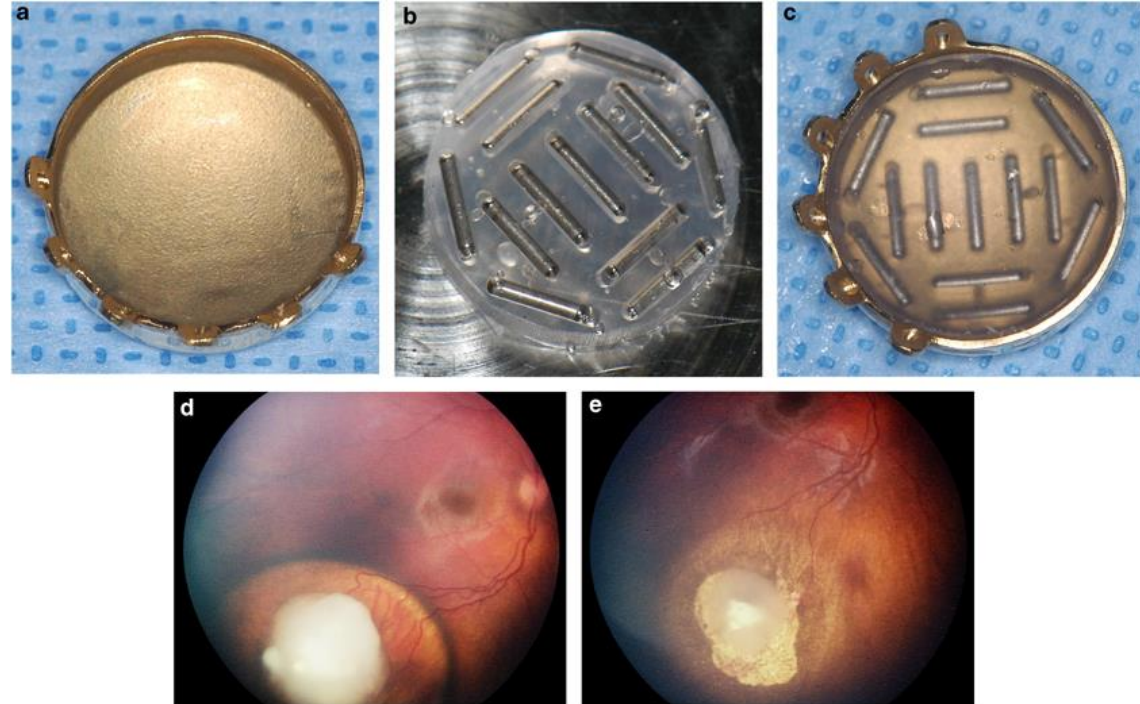
RB-Image on MRI with Optic Nerve Involvement



Aerts, I, Lumbroso-Le Rouic, L, Marion Gauthier-Villars, M, Brisse, H, Doz, F, Desjardins, L. Retinoblastoma. Orphanet Journal of Rare Diseases. 1, 31. 2006.

RB-Brachytherapy

- Seeds (LDR)
 - Please see the Khan Treatment Planning Textbook (chapter by JB) for details regarding planning.
- HDR is used in some places (outside of US more than in the US)
 - Please see the Pediatric Radiation Oncology Textbook by Kortman and Merchant (in press)
 - Copyright prevents sharing those images. Step by step images of HDR placement is shown in images.



Above, radioactive plaque with Iodine-125 seeds (c) and silicone shell (b). A gold foil prevents collateral radiation damage (a). Below, tumor before (d, showing plaque indentations) and after irradiation (e).

A. Balmer, L. Zografos, and F. Munier, ONCOGENE 25 (2006): 5341-5349.

RB – External Beam Therapy

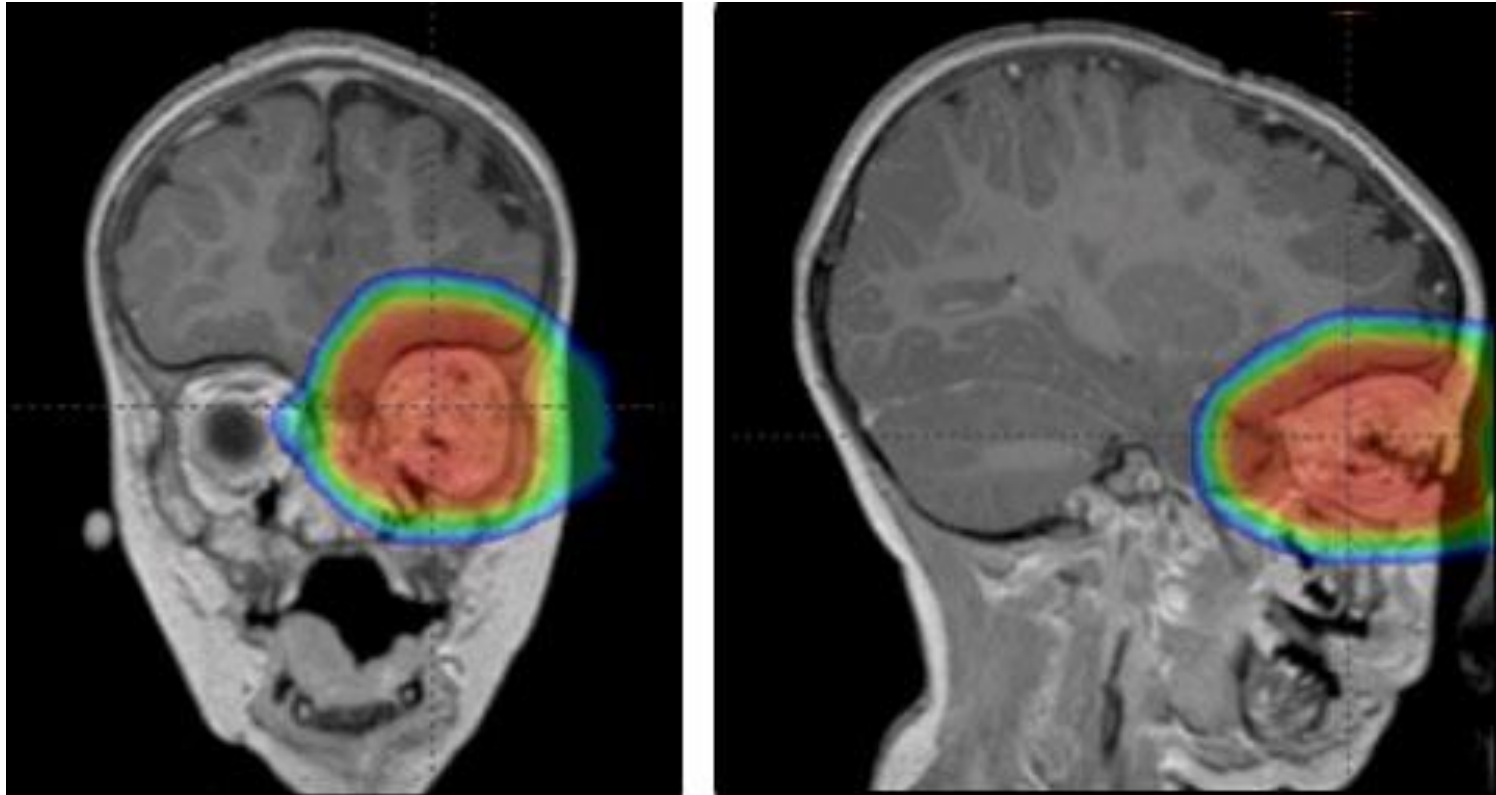


Photo from <https://www.floridaproton.org/cancers-treated/pediatric-cancer/retinoblastoma>